UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/744,625	07/16/2001	Peter Kufer	009848-0276371	3114

27500 7590 01/02/2008

PILLSBURY WINTHROP SHAW PITTMAN LLP
ATTENTION: DOCKETING DEPARTMENT
P.O BOX 10500
McLean, VA 22102

EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
01/02/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/744,625	KUFER ET AL.	
	Examiner	Art Unit	
	MISOOK YU	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,7,19-23,26 and 42-50* is/are pending in the application.

4a) Of the above claim(s) *42-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4, 6, 7, 19-23, and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Claims 42-48 remain withdrawn, and new claims 49 and 50 corresponding to groups 13, 16-20, 31, 32, and 44 in the Restriction Requirement mailed on 11/18/2003 is withdrawn. Note that applicant elected group 8, drawn to a compound comprising an antigen binding region specific for a tumor associated antigen.

Claims 1, 2, 4, 7, 19-23, 26, and 42-50 are pending.

Claims 1, 2, 4, 6, 7, 19-23, and 26 are under consideration to the extent the claims are drawn to the elected species of four functional domains, and his-tag.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, and 26 are rejected under 35 U.S.C. 102(b) as anticipated by Muller et al., (30 January 1998, a copy provided with ISR, FEBS Letters, vol. 422, pages 259-264) as evidenced by WO 97/01580 (a copy provided with ISR) in view of Shu et al., Immunotechnology 1995 Dec;1(3-4):231-41.

The claims are interpreted as drawn to a heterodimer i.e. a multifunctional compound comprising fully functional heterodimers, wherein the first polypeptides comprises CH1 domain linked to a polypeptide, and the second monomer comprises CL1 linked to a different polypeptide, wherein the heterodimer is not formed by interaction between the two polypeptides but formed by CH1 domain and CL domain, wherein said two polypeptides bind different receptors or have different ligand functions

with at least one of the polypeptide comprises a non-immunoglobulin portion having receptor or ligand function, wherein four polypeptide functional domains having different receptor or ligand functions are connected together (claim **1**), wherein claim **2** describes how the two polypeptides are linked to either said CH1 domain or said CL1 domain i.e., C-and/or-N-terminal, wherein claim **4** further limits said heterodimer to have four functional domains, wherein claim **6** further limits at least one of the two polypeptides to be a scFv-fragment, wherein claim **7** further limits at least one of the two polypeptides to have an antigen binding region specific for a tumor associated antigen, wherein claim **19** further limits said CL1 domain to be from kappa chain of an immunoglobulin, wherein claims 20-22 further limit how said CH1 domain or said CL domain is connected to the different polypeptides, namely by a polypeptide linker (claim **20**), an Ig-hinge region (claim **21**), or an IgG hinge region (claim **22**), wherein claim **26** further limits said CH1 domain be linked to a histidine tag.

Applicant argues Muller et al. fails to disclose: (1) three functional domains having different receptor or ligand functions; and (2) a non-immunoglobulin portion having receptor or ligand function. Miller et al. is deficient because the "bispecific antibodies" disclosed by Miller et al. have only two different receptor or ligand functions. It is admitted in the Office Action that Miller et al fails to disclose or suggest a non-immunoglobulin portion (OA page 6, lines 16-17). Applicants traverse the Examiner's position that Miller et al. allegedly discloses four functional domains, where this position is apparently based on construing each V. region and each VL region of each scFv as a separate functional domain (OA page 4, lines 10-15). Such a construction is clearly

precluded by Claim 1, which recites that at least one of the functional domains comprises an scFv fragment. For each scFv fragment, both the V. region and the VL region are required to provide the specific antigen-binding receptor or ligand function of the scFv fragment, such that VH regions and VL regions cannot be construed as separate functional domains. Thus, Muller et al. is deficient because the disclosed "bispecific antibodies" have only two functional domains having different receptor or ligand functions, and no non-immunoglobulin portion. Shu et al. fails to disclose: (1) the use of CL (including CK) constant domains (2) formation of heterodimers via constant domains; (3) a heterodimeric multifunctional compound; and (4) a heterodimeric multifunctional compound having at least three functional domains having different receptor or ligand functions. Shu et al discloses a single-chain fusion protein SCIg-IL-2 that forms a homodimer of polypeptide chains linked by disulfide bonds in the hinge region, each chain having a V.-VL functional domain derived from the CC49 antibody fused to C2, and IL-2 fused to C3, where the homodimer has only two different receptor or ligand function.

These arguments have been fully considered but found unpersuasive. Muller et al., teach a heterodimer comprising two monomers, wherein the first monomer comprises CH1 domain linked via C-and/or-N-terminal to two functional domains i.e. VH and VL functional domains of anti-EGF-R scFv fragment, and the second monomer comprises CL1 linked via C-and/or-N-terminal to two other functional domains i.e. VH and VL functional domains of anti-CD2 scFv fragment (total four functional domains in the multifunctional compound, as specified instant claim 4), wherein the two different

polypeptides (i.e. anti-EGF-R scFv fragment and anti-CD2 scFv fragment) lack an intrinsic affinity for one another, wherein the heterodimer is formed by a disulfide bond between the CH1 domain of the first monomer and the CL domain of the second monomer (note Fig.1, the heading "Materials and methods" at pages 259-261, and Fig. 2), wherein at least one of the two monomers is to be able to bind a tumor associated antigen (note page 259, right column, 1st paragraph, where it teaches "miniantibodies" capable of binding to the EGR receptor" that is "overexpressed by a wide range of tumors"), wherein said CL1 domain is from the kappa type chain of an immunoglobulin (note line 8 under the sub-heading "plasmid construction" at page 259, left column), wherein the CH1 domain or the CL domain is connected to the different four functional domains, at least two of the four functional domains having a ligand function to a EGF receptor (note page 259, 1st paragraph), namely by a polypeptide linker, or an Ig-hinge region, more specifically an IgG hinge region (note line 8 under the sub-heading "plasmid construction" at page 259, left column and Fig. 1B), wherein the CH1 domain is linked to a histidine tag (note line 2 from bottom of page 259, left column under the sub-heading "plasmid construction" and Fig. 1B).

The recitation of "expressed in and secreted by a mammalian host cell" in the amended claim 1 does not limit either the function and/or structure of the claimed multifunctional compound. In other words, the instant claim 1 is a product by process claim. As stated in the previous Office actions, the supporting document, WO 97/01580 demonstrates that a multifunctional compound can be made in a mammalian host cell as a secretable and fully functional heterodimer of two polypeptide chains before the

effective filing date of the instant application. WO97/01580 at page 16 especially lines 16 "a mammalian" host cell can be use to produce an engineered fully functional heterodimer antibody, and also teach at page 18 especially lines 4-20 a secretion signal that could be used in a mammalian expression system. Thus, the claimed multifunctional compound could be producible in a mammalian host cell as a secretable and fully functional heterodimer of two polypeptide chains. The Office emphasizes that WO 97/01580 is not cited to explain the structural limitation of the claimed multifunctional compound.

As stated in the previous Office actions, the recitation of a process limitation in claim 1 is not viewed as positively limiting the claimed product absent a showing that the process of making recited in claim 1 imparts a novel or unexpected property to the claimed product, as it is assumed that equivalent products are obtainable by multiple routes. The burden is placed upon the applicants to establish a patentable distinction between the claimed product and the product of the reference.

The method in which the heterodimer is produced is immaterial to its patentability. Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process in a claim is the same from the product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

Muller et al. do not teach a non-immunoglobulin portion having receptor or ligand function.

However, Shu et al., (cited above) teach making and using a non-immunoglobulin portion having receptor or ligand function (i.e. immunoglobulin-interleukin-2 fusion protein).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Muller et al., teach the heteromdimerization frame of the two polypeptides and Shu et al., teach making and using a non-immunoglobulin portion having receptor or ligand function before the effective filing date of the instant application. One of ordinary skill would have been motivated to the claimed invention because Shu et al., teach interleukin-2 brought to the site of interest by an antibody binding to a tumor antigen is good for reducing considerable systematic toxicity.

Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, 23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muller et al., (30 January 1998, a copy provided with ISR, FEBS Letters, vol. 422, pages 259-264) in view of Shu et al, (cited above) and

further in view of Pluckthun and Pack (1997, Immunotechnology, vol. 3, pages 83-105) is withdrawn.

Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, 23 and 26 are interpreted as drawn to a heterodimer i.e. a multifunctional compound comprising two monomers, wherein the first monomer comprises CH1 domain linked to a polypeptide, and the second monomer comprises CL1 linked to a different polypeptide, wherein the linking is done by the **upper hinge region of human IgG3** (claim **23**). See the interpretation of claims 1, 2, 4, 6, 7, 19, 20, 21, 22, 23 and 26 above for further details.

Applicant argues that inclusion of claims 1, 2, 4, 6, 19-22 in this rejection is not proper because these claims do not recite the upper hinge regions of human IgG. This argument has been fully considered but found unpersuasive because claim 23, which recites "the upper hinge regions of human IgG" depends on claim 22, which in turn depends on claim 20, etc. Although the claims do not specifically recite the very specific linker, those claims also include the linker recited in claim 23. Otherwise, it would not a depend claim.

As for applicant's second argument that the 103 analysis is not done properly following the TSM test, the claimed invention is obvious based on the knowledge generally available to one of ordinary skill in the art

Muller et al., teach a multifunctional compound comprising two monomers, wherein the first monomer comprises CH1 domain linked to a polypeptide, and the second monomer comprises CL1 linked to a different polypeptide with all the structural limitations of claims 1, 2, 4, 6, 7, 19, 20, 21, 22, and 26. Muller et al., at the last

sentence under the heading "Introduction" also teach why one of ordinary skill would be motivated to use a human sequence i.e. to reduce immunogenicity in a human subject.

Muller et al., a non-immunoglobulin portion having receptor or ligand function. Muller et al., or do not specifically teach "the upper hinge region of human IgG3".

However, Shu et al., (cited above) teach making and using a non-immunoglobulin portion having receptor or ligand function (i.e. immunoglobulin-interleukin-2 fusion protein), and Pluckthun and Pack teach at page 89, left column, 1st paragraph "the use of hinge regions creates a spacing, hinge bending and rotational freedom of the associated scFv fragments, similar to the Fv-arms of a complete antibody...but with a fraction of its molecular weight. This was achieved by not adding the dimerization handle directly to the scFv fragment, but rather separated **by the upper hinge** from murine or **human Ig3**, known to lead to a flexible arrangements of domains". Further, Pluckthun and Pack teach at the paragraph bridging pages 95-96 that a human IgG hinge region has been used for therapeutic application, which requires reduced "immunogenicity" in a human clinical application.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a

reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to substitute the linkers of Muller et al., with the upper hinge region of human IgG3 taught by Pluckthun and Pack, to make a multifunctional compound. This would have been accomplished with a reasonable expectation of success since combination of Muller et al., (Jan. 1998) and Pluckthun and Pack (1997) teach how to make each elements of the claimed invention. One of ordinary skill in the art would have been motivated to make and use the claimed multifunctional compound using the upper hinge region of human IgG3 as the linker because Pluckthun and Pack teach that the upper hinge region of human IgG3 is good for reducing immunogenicity in a human patient and the human IgG3 is also good for its flexibility.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MISOOK YU
Primary Examiner
Art Unit 1642

/Misook Yu/